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Intralesional Macular Atrophy in Anti–Vascular Endothelial Growth Factor Therapy for Age-Related Macular Degeneration in the IVAN Trial

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Purpose: To report on the development and progression of macular atrophy (MA) and its relationship with morphologic and functional measures in study and fellow eyes in the Inhibition of vascular endothelial growth factor (VEGF) in Age-related Choroidal Neovascularisation trial.

Design: Reading center analysis of data from a randomized controlled trial.

Participants: Participants with previously untreated neovascular age-related macular degeneration (nAMD) in the study eye.

Methods: Color, fluorescein angiography (FA) and OCT images acquired at baseline and during the 2-year follow-up were graded systematically for presence of MA. Regression models were constructed to explore relationships between MA and lesion morphology and vision measures (best-corrected distance and near acuity, reading speed and index, contrast sensitivity).

Main Outcome Measures: Primary outcome was development of intralesional MA (≥175 μm greatest linear dimension of choroidal vessels seen on FA and/or color, aided by OCT) lying within the maximum footprint of the neovascular lesion.

Results: Study eye data were available for 594 of 610 participants; 57 (9.6%) showed intralesional MA at baseline. Incident intralesional MA occurred in 24.4% by the final visit and extralesional MA in only 1.54%. In fellow eyes, an established nAMD lesion was present at baseline in 248 of whom 42 (16.9%) showed intralesional MA at baseline and 32 (12.9%) developed incident intralesional MA. The odds of incident intralesional MA by final visit were lower in study eyes that had ≥50% classic CNV at baseline (odds ratio [OR], 0.39; 95% confidence interval [CI], 0.19–0.80; $P = 0.010$), subretinal fluid at final visit (OR, 0.41; 95% CI, 0.25–0.76; $P = 0.004$), or pigment epithelial detachment at final visit (OR, 0.40; 95% CI, 0.21–0.74; $P = 0.004$). Secondary analyses of incident or progressed intralesional MA in study eyes supported these findings, with odds increasing if the fellow eye had baseline intralesional MA (OR, 2.43; 95% CI, 1.09–5.44; $P = 0.030$). No significant associations were observed between development of intralesional MA and any other morphologic or visual function measure.

Conclusions: Macular atrophy frequently develops within an nAMD lesion in eyes receiving anti–VEGF therapy over 2 years. No associations between incident MA and drug or treatment frequency or visual function were detected, providing some reassurance to clinicians; however, the longer-term effects remain unknown. *Ophthalmology 2019;126:75-86 © 2018 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

Supplemental material available at www.aaojournal.org.

The treatment of neovascular age-related macular degeneration (nAMD) has been transformed by the introduction of intraocular therapies that inhibit vascular endothelial growth factor (VEGF). As increasing numbers of anti-VEGF injections are delivered over longer periods in clinical care for nAMD, there is much interest in potential ocular adverse effects.

The Inhibition of VEGF in Age-Related Choroidal Neovascularisation (IVAN) trial[1,2] compared 2 anti-VEGF agents and 2 regimens in previously untreated eyes with nAMD in a 2-way factorial randomized trial. The IVAN trial reported higher proportions of geographic atrophy (GA) in eyes allocated to the continuous regimen (median, 23 injections) compared with the discontinuous regimen (median, 13 injections; odds ratio [OR], 1.47; $P = 0.03$). No difference was detected between the 2 drugs with respect to the proportion of eyes with GA at 2 years. Similar findings were reported in the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT)[3–6] and confirmed in meta-analyses by

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us.[7] These findings have led to a debate over whether overexposure to anti-VEGF agents could cause atrophy in the macula, contributing to poor visual outcome. Alternatively, the neovascular process itself could create the conditions for atrophy. Unfortunately, these and other studies have reported on atrophy within the macula without characterizing the location of the atrophic region with respect to the neovascular lesion.

We conducted a revised grading of the image repository in the IVAN trial to explore the effect of clinical and morphologic predictors on the development and extent of macular atrophy (MA) in study eyes. We carefully defined the location of MA and studied it in relation to the lesion footprint, a topic that to date has not been studied. Additionally, we reviewed fellow eyes with lesions at baseline for comparison with development of intralesional MA in eyes with untreated lesions.

Methods

Full details of the data collection in IVAN are available elsewhere.[7] Of particular relevance to the analysis presented herein, measures of visual function were performed by trained and accredited observers using a full refraction protocol, standardized charts, and illumination comprising distance best-corrected visual acuity (BCVA) recorded as letters read on an Early Treatment Diabetic Retinopathy Study chart at 1 m, contrast sensitivity (CS) as letters read at 1 m on a Pelli Robson chart, near VA measured in logarithm of the minimum angle of resolution units using the Bailey Lovie near chart at 25 cm, Belfast reading speed at 25 cm, and reading index calculated as a function of print size.[8] OCT images were captured using Stratus (Carl Zeiss AG, Oberkocken, Germany) or Spectralis (Heidelberg Engineering, Heidelberg, Germany) platforms. Institutional review board or ethics committee approval was obtained (identifier, 07/NIR03/37), the trial was registered (identifier, ISRCTN92166560), and all participants gave informed consent.

Grading

Retinal images were graded systematically by trained and accredited graders in the Network of Reading Centres UK against a revised protocol developed specifically for this study. The border of the active neovascular complex (classic and occult choroidal neovascularization, retinal angiomatous proliferation, associated elevated blocked fluorescence) was outlined at baseline, intervening, and final visits and the maximum lesion footprint was determined.

We defined MA as the presence of any of the following features on multimodal imaging:

1. Color: an area of pallor with 2 of the following: clearly defined margins, scalloped margins, identifiable large choroidal vessels.
2. Fluorescein angiography (FA): area of hyperfluorescence that persisted throughout the run (sometimes fading in the late phase) with identifiable large choroidal vessels.
3. OCT: increased transmission of the light signal into the choroid and thinning or absence of the outer retinal layers. On higher-quality or higher-resolution scans, the following additional features of MA could be used: dipping of the photoreceptor nuclear layer toward the retinal pigment epithelium (RPE)−Bruch's membrane complex, absence of photoreceptor inner and outer segments, thinning of RPE−Bruch's complex, and absence of the choriocapillaris profile.

Macular atrophy was identified, segmented, and measured on FA images (or color where FA was not available) in 7 of 596 eyes (1.2%) at baseline and in 103 of 596 (17.3%) at the final visit and was considered present if the combined greatest linear dimension of the delineated area was 175 μm or more. The footprint of the neovascular lesion was outlined on the FA at the 3 visits where this was captured (baseline, month 12, and month 24). OCT features were used to aid in identification of MA; if seen on OCT but not other modalities images were reviewed at arbitration where a senior clinician (including U.C., T.P.) decided if atrophy was present and localized it to the en face FA image. Graders specified the location of MA as within (intralesional) based on the maximum lesion footprint. Macular atrophy outside the lesion boundary was considered intralesional if it was contiguous. The Wisconsin Age-related Maculopathy Grading System definition of GA[9] was used only for extralesional MA in addition to the greatest linear dimension criterion, that is, at least 2 of the following: visibility of choroidal vessels, well-defined margins, and scalloped edges. All lesion area measurements were in square millimeters, and the presence of other FA and OCT measures was recorded. Baseline hemorrhage was assessed on color images, and subretinal fluid (SRF) and pigment epithelial detachment (PED) were assessed on OCT. Examples from the IVAN study showing intralesional MA within the maximum footprint of the active neovascular complex are shown for progression and development in Figures 1 and 2, respectively, with 1 additional example for each in Supplemental Figures S1 and S2 (available at www.aaojournal.org).

Analysis

Eyes were classified by the presence of intralesional MA as follows: no intralesional MA at baseline or final visit, intralesional MA developed between baseline and final visit, or intralesional MA present at both visits. For fellow eyes, which could have received no previous treatment or could have received previous verteporfin photodynamic, anti-VEGF therapy, or both, the presence or absence of an nAMD lesion at baseline was determined. The analysis did not include the 19 study eyes that showed GA (extralesional MA) only at baseline and 3 that showed none at baseline and GA only at follow-up, nor the 14 fellow eyes that showed GA only at baseline and the 5 eyes that showed none at baseline and GA only at follow-up.

The primary outcome was defined as incident intralesional MA. Defining the primary outcome as incident intralesional MA meant that the primary analysis excluded study eyes with intralesional atrophy at baseline. In a secondary analysis, eyes with intralesional MA at baseline were divided according to whether the area of intralesional MA had increased by 20% or more between visits, denoting progression, or not (see Supplemental Methods, available at www.aaojournal.org). This cutoff point was chosen because the proportion classified as progressing did not vary when the cutoff point was changed to a 50% or more. Other secondary outcomes included area of intralesional MA (in square millimeters), distance and near BCVA, near VA, CS, reading speed and reading index.

We defined a secondary outcome of incident or progressed intralesional MA so we could add in study eyes with intralesional MA at baseline and investigate relationships with MA progression. As well as testing the generalizability of the primary outcome relationships, this analysis also had more statistical power.

Demographics, treatment groups, morphologic features, and visual function measures were summarized by lesion atrophy status. Linear regression was used to analyze the effect of study eye lesion development on visual function metrics at the final visit;

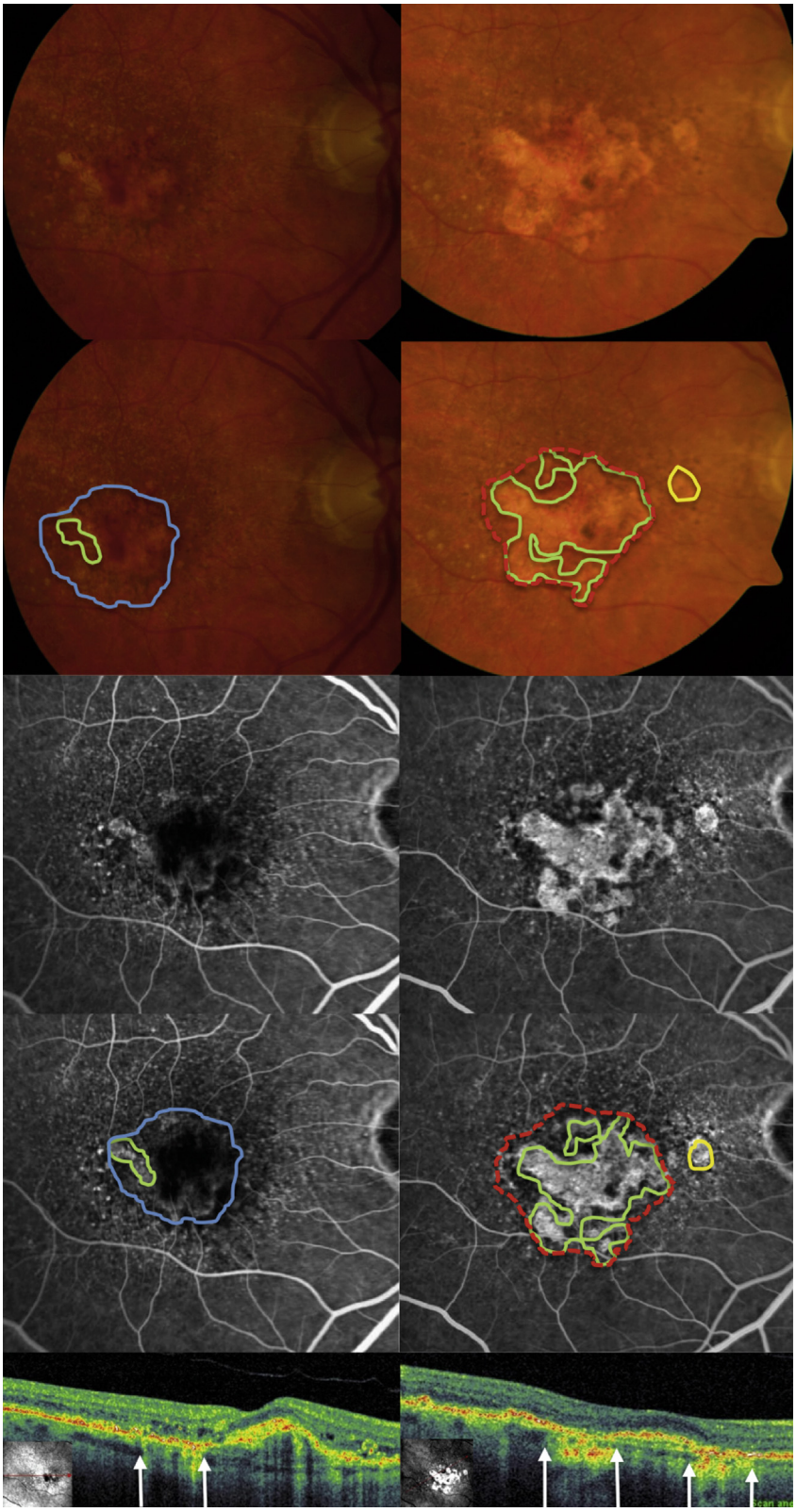

Figure 1. Example of a case of progression of intralesional macular atrophy (MA) with clean and annotated images. **Left column**, Baseline lesion shows fibrovascular pigment epithelial detachment (FPED, type 1 lesion) with a small zone of MA. **Right column**, By the final visit (24 months), the zone of intralesional MA has expanded at the site of partial involution of the FPED and a new zone of geographic atrophy (extralesional MA) has developed. Note that the lesion footprint and features were segmented and measured from FA images. The color annotations are to aid interpretation. Blue line = total lesion footprint at baseline; green line = intralesional MA; yellow line = extralesional MA; red broken line = maximum lesion footprint; white arrows = boundaries of MA on OCT.

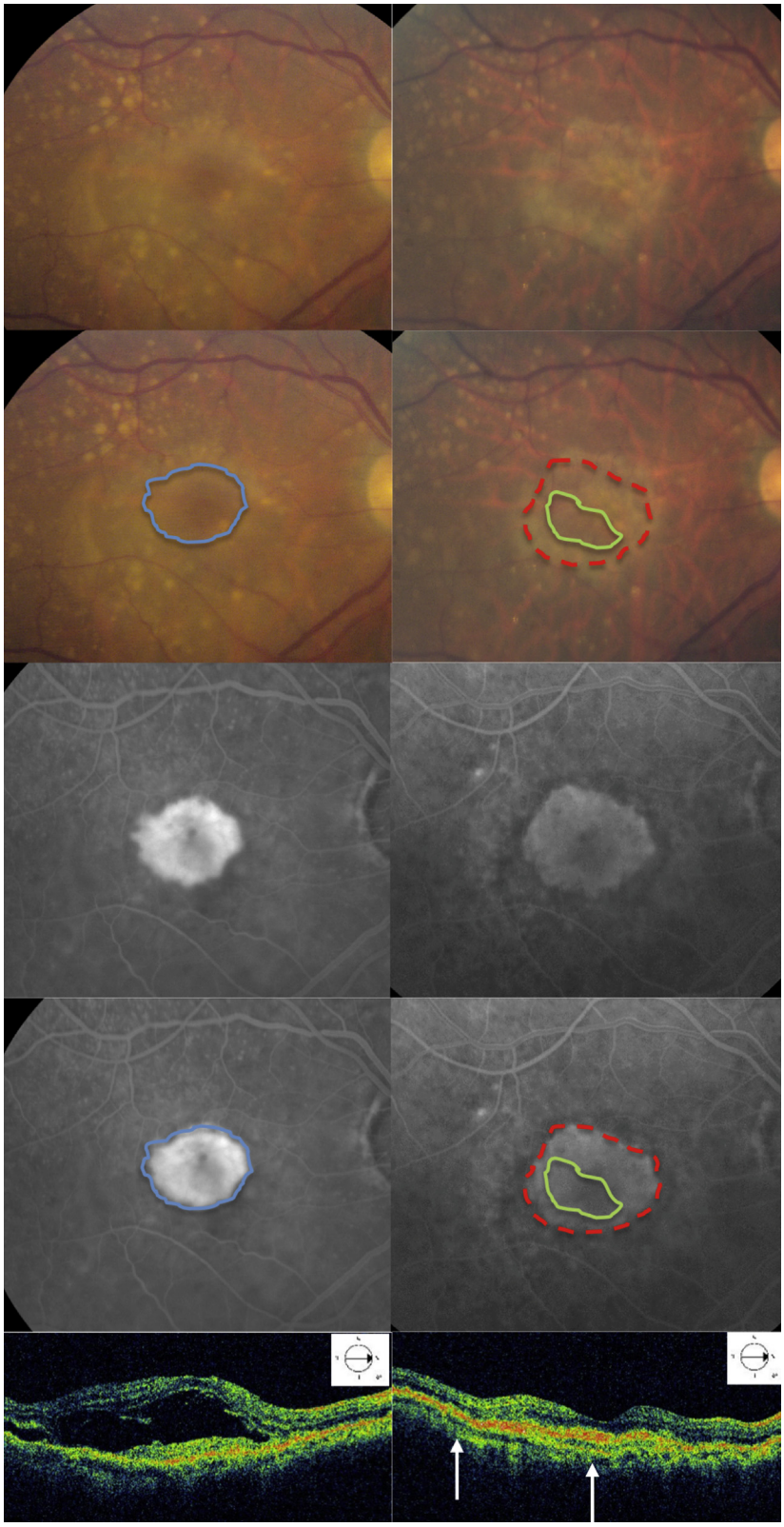

Figure 2. Example of a case of development of intralesional macular atrophy (MA) with clean and annotated images. **Left column**, Baseline lesion shows classic no occult (type 2) lesion. **Right column**, By the final visit (24 months), the lesion has increased slightly and involuted and a zone of intralesional MA has developed. Note that the lesion footprint and features were segmented and measured from FA images. The color annotations are to aid interpretation. Blue line = total lesion footprint at baseline; green line = intralesional MA; red broken line = maximum lesion footprint; white arrows = boundaries of MA on OCT.

Table 1. Macular Atrophy Status at Baseline and Final Visit for Study Eyes and Fellow Eyes with a Neovascular Age-Related Macular Degeneration Lesion at Baseline

	Final Visit				
Baseline	*None*	*Extralesional*	*Intralesional*	*Both*	**Total**
Study eyes					
None	390	3	122	5	520
Extralesional	0	11	0	8	19
Intralesional	0	0	56	1	57
Total	390	14	178	14	596
Fellow eyes with a lesion at baseline					
None	159	5	24	1	189
Extralesional	0	10	0	4	14
Intralesional	0	0	40	2	42
Both	0	0	0	3	3
Total	159	15	64	10	248

these analyses were adjusted for baseline visual function and included only eyes for which data for all model covariates were available. The effect of demographic, study, and morphologic characteristics on development of intralesional MA in both eyes was assessed using logistic regression, and the effect of these factors on the area of intralesional MA in the study eye was assessed using linear regression. Treatment frequency was fitted as a continuous predictor and was presented as the effect of 3 injections, that is, 1 treatment cycle.

Results

All 610 patients recruited to the IVAN trial were considered for inclusion. Data on GA or intralesional MA were missing for 14 study eyes that were excluded, leaving 596 for the analyses. Table 1 shows the atrophy status for study and fellow eyes at baseline and final visits; 514 final visits (86%) were at month 24. At baseline,

Table 2. Demographic Features, Treatment, and Key Lesion-Related Risk Factors by Study Eye Status for Intralesional Macular Atrophy

	No Intralesional Macular Atrophy at Baseline or Final Visit (n = 390)		**No Intralesional Macular Atrophy at Baseline; Developed by Final Visit (n = 127)**		**Intralesional Macular Atrophy at Baseline and Final Visit (n = 57)**		**Overall (n = 574)**	
	No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
Demographic features								
Age (yrs)	Mean, 77.0	SD, 7.6	Mean, 78.7	SD, 6.7	Mean, 78.7	SD, 7.6	Mean, 77.5	SD, 7.5
Gender	163/390	41.8	49/127	38.6	20/57	35.1	232/574	40.4
Drug and treatment frequency								
Bevacizumab	188/390	48	59/127	46	32/57	56	279/574	49
Treatment frequency	Median, 19	IQR, 12–23	Median, 19	IQR, 11–23	Median, 21	IQR, 13–23	Median, 19	IQR, 12–23
≤3 injections	14/390	3.6	8/127	6.3	1/57	1.8	23/574	4.0
Lesion metrics								
Area of baseline intralesional MA (mm^2)					Median, 0.7	IQR, 0.3–2.2	Median, 0.7	IQR, 0.3–2.2
Area of final visit intralesional MA (mm^2)			Median, 1.3	IQR, 0.6–4.5	Median, 3.1	IQR, 1.3–4.8	Median, 2.0	IQR, 0.7–4.7
Area of intralesional MA increased by ≥20%					36/56	64.3	36/56	64.3
SRF at baseline	301/355	84.8	97/117	82.9	32/50	64.0	430/522	82.4
SRF at final visit	146/369	39.6	20/122	16.4	7/55	12.7	173/546	31.7
PED at baseline	269/357	75.4	99/119	83.2	41/50	82.0	409/526	77.8
PED at final visit	323/373	86.6	91/123	74.0	41/56	73.2	455/552	82.4
Hemorrhage at baseline	223/384	58.1	83/125	66.4	37/57	64.9	343/566	60.6
Baseline CNV								
Occult (<50% of lesion area classic)	264/372	71.0	106/124	85.5	47/52	90.4	417/548	76.1
Classic (>50% of lesion area classic)	108/372	29.0	18/124	14.5	5/52	9.6	131/548	23.9
Fellow eye								
Baseline intralesional MA								
No lesion	224/387	57.9	76/126	60.3	28/57	49.1	328/570	57.5
Lesion with no MA	144/387	37.2	36/126	28.6	19/57	33.3	199/570	34.9
Lesion with MA	19/387	4.9	14/126	11.1	10/57	17.5	43/570	7.5
Baseline atrophy outside the lesion	21/387	5.4	26/126	20.6	13/57	22.8	60/570	10.5

CNV = choroidal neovascularization; IQR = interquartile range; MA = macular atrophy; PED = pigment epithelial detachment; SD = standard deviation; SRF = subretinal fluid.
Missing data as follows, number of patients (no lesion atrophy at baseline or final visit, lesion atrophy at final visit but not baseline, lesion atrophy at baseline and final visit): baseline area of atrophy, 1 (—, —, 1); final visit area of atrophy, 1 (—, 0, 1).

Table 3. Clinical Measures of Vision in the Study Eye by Presence or Absence of Intralesional Macular Atrophy at Baseline and Final Visit

	No Intralesional Macular Atrophy at Baseline or Final Visit (n = 390)		No Intralesional Macular Atrophy at Baseline; Developed by Final Visit (n = 127)		Intralesional Macular Atrophy at Baseline and Final Visit (n = 57)		Overall (n = 574)	
	Median	*Interquartile Range*	*Median*	*Interquartile Range*	*Median*	*Interquartile Range*	*Median*	*Interquartile Range*
Baseline								
BCVA	66	54–74	61	50–69	64	55–73	65	52–73
Near VA	0.6	0.4–0.8	0.7	0.5–0.9	0.6	0.4–0.8	0.6	0.4–0.9
CS letters	28	23–31	28	23–30	26	23–29	28	23–30
Reading speed	46.9	31.1–63.2	41.7	24.0–59.0	39.5	26.0–55.4	44.7	29.6–61.0
Reading index	39.7	16.7–78.3	28.3	11.0–45.6	42.1	19.2–64.0	37.3	14.9–69.9
Vision too poor to read*	n = 3	0.8%	n = 0	0.0%	n = 2	3.6%	n = 5	0.9%
Final visit								
BCVA	73	59–80	68	53–78	69	50–79	72	56–80
Near VA	0.4	0.3–0.7	0.5	0.3–1.0	0.5	0.3–0.9	0.4	0.3–0.7
CS letters	30	26–32	29	25–32	28	24–32	29	25–32
Reading speed	44.7	25.5–66.8	35.6	18.5–52.7	33.9	19.7–54.5	42.0	23.4–62.1
Reading index	59.9	23.4–95.2	39.2	8.6–64.1	40.3	11.4–81.4	52.1	15.6–92.3
Vision too poor to read*	n = 7	2.1%	n = 3	2.7%	n = 1	2.0%	n = 11	2.2%
Change from baseline								
BCVA	5	−2 to 12	6	0–14	2	−6 to 11	5	−2 to 12
Near VA	−0.1	−0.3 to 0.1	−0.1	−0.3 to 0.1	−0.1	−0.2 to 0.3	−0.1	−0.3 to 0.1
CS letters	1	−1 to 5	1	−2 to 5	0	−2 to 5	1	−2 to 5
Reading speed	−2.3	−20.5 to 11.7	−4.0	−20.3 to 10.4	−4.9	−24.0 to 9.9	−3.0	−20.5 to 10.8
Reading index	5.3	−11.6 to 38.1	3.2	−11.9 to 29.0	−1.0	−25.3 to 23.9	3.9	−12.3 to 36.1
Vision too poor to read*	n = 10	3.0%	n = 3	2.8%	n = 3	6.0%	n = 16	3.3%

BCVA = best-corrected visual acuity; CS = contrast sensitivity; VA = visual acuity.
Missing data as follows, patients (no lesion atrophy at baseline or final visit, lesion atrophy at final visit but not baseline, lesion atrophy at baseline and final visit): baseline near VA, 4 (3, 0, 1); baseline reading speed, 30 (21, 5, 4); baseline reading index, 30 (21, 5, 4); final visit BCVA, 1 (1, 0, 0); final visit near VA, 55 (37, 13, 5); final visit CS letters, 47 (30, 13, 4); final visit reading speed, 81 (56, 18, 7); final visit reading index, 81 (56, 18, 7); change from baseline BCVA, 1 (1, 0, 0); change from baseline near VA, 57 (38, 13, 6); change from baseline CS letters, 47 (30, 13, 4); change from baseline reading speed, 100 (68, 22, 10).
*Vision classed as too poor to read if near VA = 1.6.

19 study eyes showed GA only and 57 showed intralesional MA; none showed both. By the final visit, 25.0% of study eyes (130/520) that were free of atrophy at baseline demonstrated new MA: 3 cases were extralesional, 122 cases were intralesional, and 5 cases were both. The remaining study eyes that showed no atrophy at baseline also were free of atrophy at the final visit (n = 390). Over the course of the trial, the overall frequency of intralesional MA rose from 9.6% (57/596) to 32.2% (192/596).

Neovascular age-related macular degeneration lesions were present at baseline in 42.0% of fellow eyes (248/591); this information was missing for 5 patients. Of the 248 eyes, 42 eyes showed intralesional MA only, 14 eyes showed extralesional MA only, and 3 eyes showed both. By the final visit, 30 fellow eyes demonstrated new MA: 5 cases were extralesional, 24 cases intralesional, and 1 case was both. The frequency of intralesional MA in fellow eyes with a neovascular lesion at baseline rose from 16.9% (42/248) to 25.8% (64/248). Patient demographic features, drug and treatment frequency, and key lesion metrics by study eye intralesional MA status are shown in Table 2. Functional metrics by study eye intralesional MA status are shown in Table 3.

Images from all 3 methods were available for 545 of 596 study eyes (91%) at baseline and for 477 of 596 study eyes (80%) at follow-up. At baseline, 589 eyes (99%) had undergone FA, 590 eyes (99%) had undergone color, and 551 eyes (92%) had undergone OCT. At follow-up, 493 eyes (83%) had undergone FA, 590 eyes (99%) had undergone color, and 576 eyes (97%) had undergone OCT.

Primary Outcome

Figure 3 shows the relationship between several patient-, eye-, and treatment-related predictors and the development of incident intralesional MA in study eyes with no intralesional MA at baseline. There was no statistically significant difference in the odds of incident intralesional MA between eyes treated with bevacizumab compared with those treated with ranibizumab (OR, 0.995; 95% confidence interval [CI], 0.81–1.63; $P = 0.98$); the number of cycles of treatment (closely related to discontinuous vs. continuous allocation in the IVAN trial) also had no effect (OR, 1.01 per treatment cycle; 95% CI, 0.91–1.13 per treatment cycle; $P = 0.83$). The presence of SRF, PED, and hemorrhage at baseline also were not related to the odds of incident intralesional MA.

In study eyes in which classic CNV accounted for more than 50% of the lesion area at baseline, the odds of intralesional MA developing by the final visit were reduced significantly compared with eyes in which classic CNV accounted for 50% or less of the lesion area at baseline (OR, 0.39; 95% CI, 0.19–0.80; $P = 0.010$). The presence of SRF at the final visit and PED at the final visit (but not at baseline) independently reduced the odds of intralesional MA developing (OR, 0.41; 95% CI, 0.23–0.76; and OR, 0.40; 95% CI, 0.21–0.74, respectively; $P = 0.004$ for both). The presence of intralesional MA or extralesional MA (atrophy outside the lesion) in the fellow eye at baseline both independently increased the odds of incident intralesional MA in the study eye (OR, 2.34;

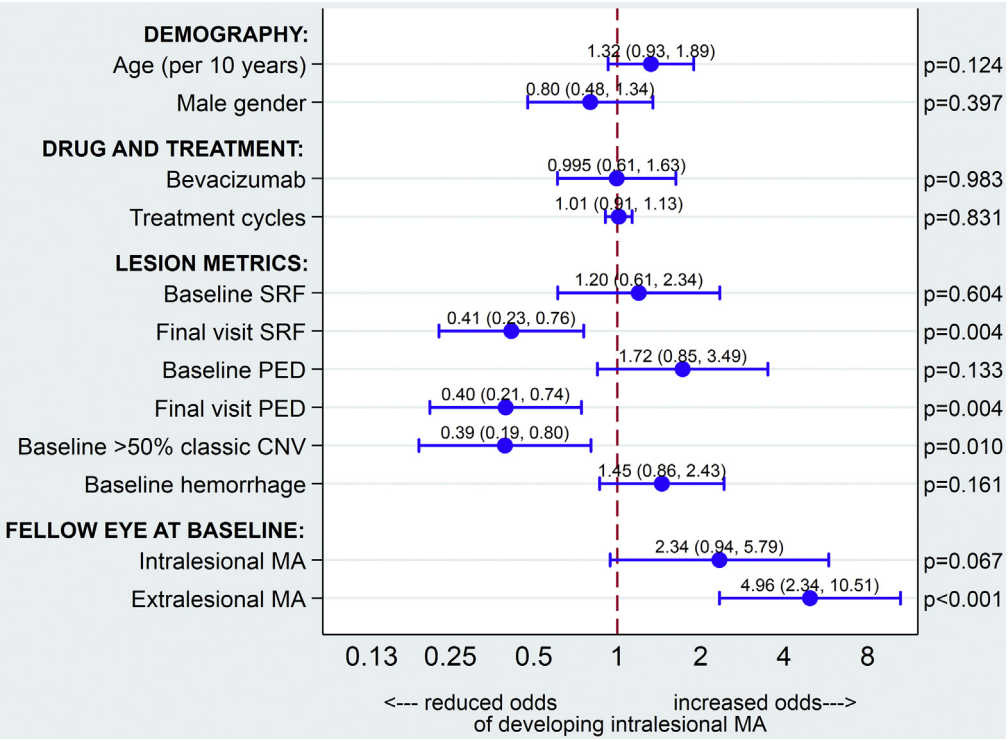

Figure 3. Graph showing the relationship between risk factors and the development of intralesional macular atrophy (MA). The model included 425 study eyes with no intralesional MA at baseline, all with no missing data, of whom 106 demonstrated intralesional MA by the final visit. Treatment cycles (1 cycle = 3 injections) separate continuous from discontinuous regimens. CNV = choroidal neovascularization; PED = pigment epithelial detachment; SRF = subretinal fluid.

95% CI, 0.94−5.79; $P = 0.07$; and OR, 4.96; 95% CI, 2.34−10.51; $P < 0.001$, respectively).

Figure 4 shows the same analysis of factors for intralesional MA in study eyes (Fig 3), but for the secondary outcome, that is, incident or progressed intralesional MA. Including more study eyes improved the precision of the effect estimates. The pattern of the results was very similar: odds ratios were 0.31 for 50% or less classic CNV at baseline, 0.36 for presence of SRF at final visit, 0.45 for presence of PED at final visit, 2.43 for presence of intralesional MA in the fellow eye at baseline, and 5.27 for atrophy outside the lesion in the fellow eye at baseline.

Figure S3 (available at www.aaojournal.org) shows the analysis of the effects of the same factors, but on the secondary outcome of intralesional MA area. This analysis supported the negative association between SRF and intralesional MA at the final visit; the area of intralesional MA was approximately one third less when SRF was present compared with when absent (geometric mean ratio, 0.66; 95% CI, 0.35−1.24; $P = 0.198$). Finally, the total area of intralesional MA was significantly larger in patients with intralesional MA at baseline in the fellow eye (geometric mean ratio, 3.07; 95% CI, 1.54−6.11; $P = 0.002$).

With respect to differences in visual function secondary outcomes (Table 3), among study eyes free of lesion atrophy at baseline, there were no statistically significant differences between eyes in which MA developed during the study and eyes in which it did not: final visit BCVA (−0.72 letters; 95% CI, −3.58 to 2.40 letters; $P = 0.62$), near VA (0.066; 95% CI, −0.004 to −0.136; $P = 0.07$), CS (−0.24 units; 95% CI, −1.29 to 0.80 units; $P = 0.65$), reading speed (−3.86 units; 95% CI, −8.94 to 1.21 units; $P = 0.14$), or reading index (−4.46; 95% CI, −13.66 to 4.73; $P = 0.34$). Although the difference in mean near VA at final visit between the 2 groups reached borderline statistical significance, there was no indication of any difference in medians, and we suspect this difference arises because of outliers.

Figure 5 shows the relationship between a subset of the factors studied (only those available, and relevant to fellow eyes) and incident intralesional MA in 184 fellow eyes with nAMD lesions present at baseline and no intralesional MA (Table 4). Data were excluded for 5 patients who showed extralesional MA only at follow-up. The presence of intralesional MA at baseline in the study eye was associated with increased odds of incident intralesional MA in the fellow eye (OR, 3.35; 95% CI, 1.04−10.77; $P = 0.04$). Age, gender, and study eye treatment did not significantly affect development of incident intralesional MA in the fellow eye.

Discussion

We report the findings of a detailed analysis of the clinical and imaging dataset collected during the IVAN trial. Macular atrophy within the lesion develops or progresses in just less than one third of eyes being treated with intravitreal anti-VEGF therapy and occurred at a higher frequency than might be expected from natural history. However, prevalent and incident intralesional MA did not result in a significantly greater reduction in measures of visual function during the study. There was no evidence to suggest that trial allocation to drug or treatment frequency affected the incidence of intralesional MA.

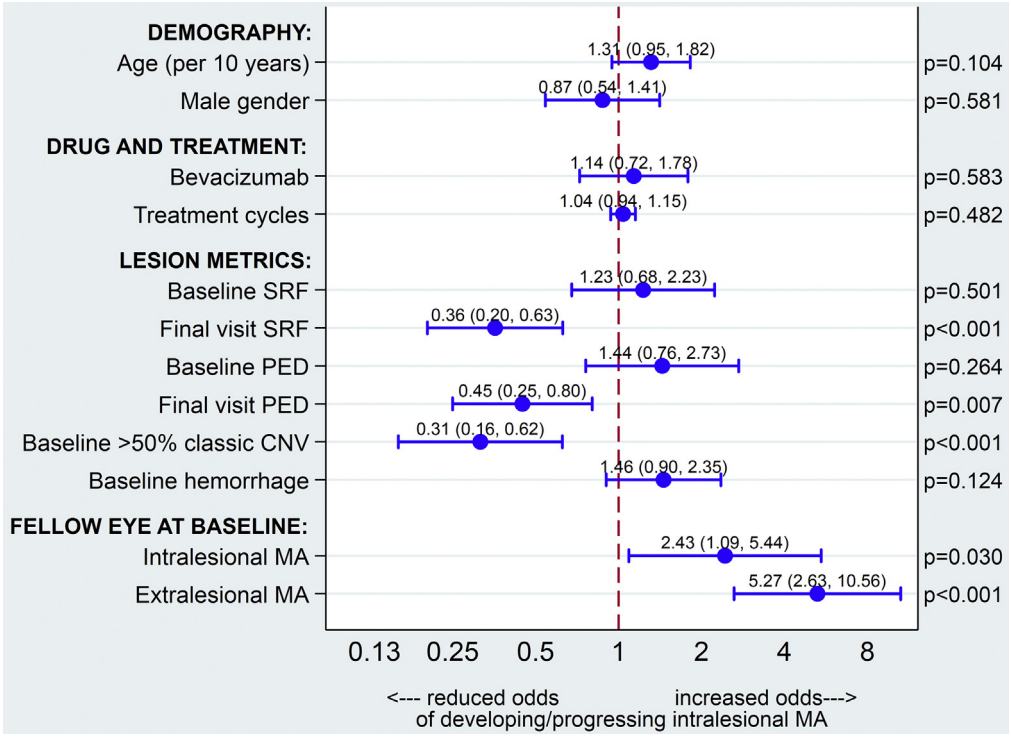

Figure 4. Graph showing the relationship between risk factors and incident or progressed intralesional macular atrophy (MA) in study eyes. The reference group was eyes with no intralesional MA combined with those in which intralesional MA did not increase by final visit (n = 319 + 13). The comparator group was study eyes with incident or progressed intralesional MA at the final visit (n = 106 + 29). Treatment cycles (1 cycle = 3 injections) separate continuous from discontinuous regimens. CNV = choroidal neovascularization; PED = pigment epithelial detachment; SRF = subretinal fluid.

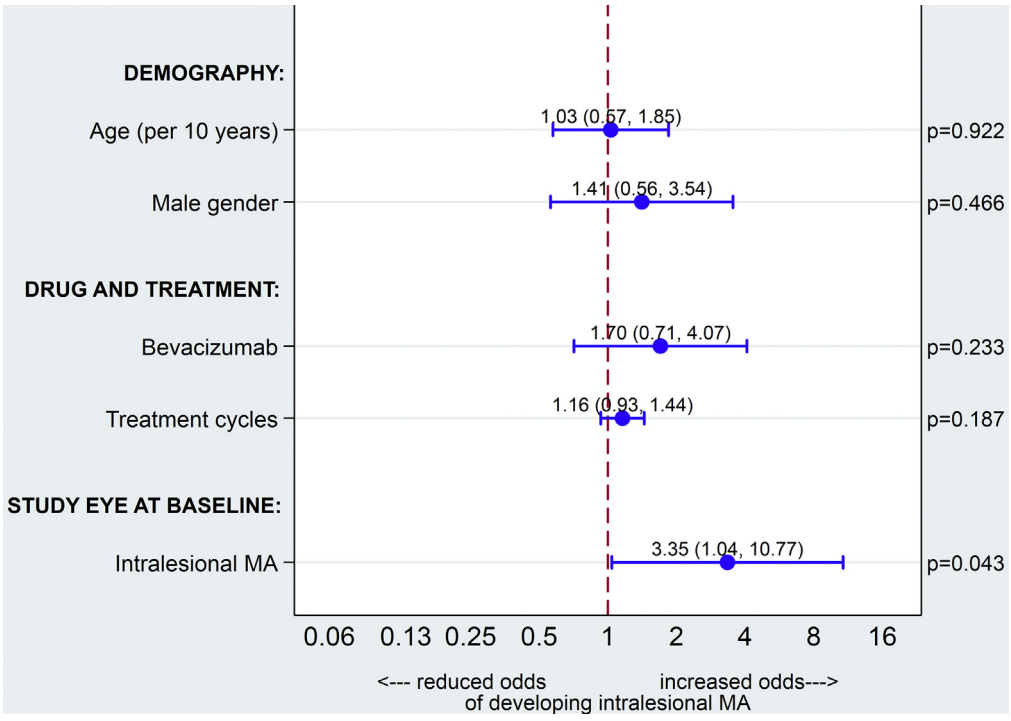

Figure 5. Graph showing the model exploring risk factor associations in the development of intralesional macular atrophy (MA) in 184 fellow eyes with neovascular lesions with no missing data; 25 fellow eyes were classified as demonstrating MA by final visit. Treatment cycles (1 cycle = 3 injections) separate continuous from discontinuous regimens.

Table 4. Clinical Measures of Vision in the Fellow Eye by Presence or Absence of Intralesional Macular Atrophy at Baseline and Final Visit

	Fellow Eye Free of Neovascular Age-Related Macular Degeneration (n = 343)		Neovascular Lesion Present, No Atrophy at Baseline or Final Visit (n = 159)		Neovascular Lesion Present, No Atrophy at Baseline; Developed by Final Visit (n = 25)		Neovascular Lesion Present, Atrophy at Baseline and Final Visit (n = 45)		Overall (n = 572)	
	Median	*Interquartile Range*	*Median*	*Interquartile Range*	*Median*	*Interquartile Range*	*Median*	*Interquartile Range*	*Median*	*Interquartile Range*
Baseline										
BCVA	81	74–85	59	19–73	55	40–76	41	17–68	75	59–84
Near VA	0.3	0.2–0.4	0.6	0.3–1.2	0.6	0.3–1.0	0.9	0.5–1.4	0.3	0.2–0.6
CS letters	32	29–35	25	11–30	27	23–29	23	7–27	30	25–34
Reading speed	60.0	45.0–75.0	47.7	28.0–63.2	42.0	25.7–62.1	37.6	14.2–52.5	54.5	38.2–70.6
Vision too poor to read* (n, %)	n = 1	0.3%	n = 12	9.5%	n = 0	0.0%	n = 4	12.5%	n = 17	3.3%
Area of intralesional MA (mm^2)							3.8	1.4–9.9	3.8	1.4–9.9
Final visit										
BCVA	81	74–86	51	17–73	57	33–72	35	15–59	75	53–83
Near VA	0.3	0.2–0.4	0.6	0.3–1.3	0.7	0.5–1.4	1.0	0.5–1.5	0.3	0.2–0.7
CS letters	31	28–35	24	13–30	26	21–30	22	9–29	30	24–34
Reading speed	55.4	36.5–73.5	32.2	17.5–57.6	33.8	21.5–43.0	29.0	13.0–48.9	48.3	28.9–69.2
Vision too poor to read* (n, %)	n = 3	1.0%	n = 10	9.1%	n = 3	13.0%	n = 6	18.2%	n = 22	4.7%
Area of intralesional MA (mm^2)					1.9	1.0–4.2	4.4	1.8–9.7	3.5	1.1–8.7
Area increased by ≥20%							16/40	40%	16/40	40%

BCVA = best-corrected visual acuity; CS = contrast sensitivity; MA = macular atrophy; VA = visual acuity.
Missing data as follows, number of patients (no baseline lesion, no atrophy at baseline or final visit, atrophy at final visit but not baseline, atrophy at baseline and final visit): baseline BCVA, 11 (1, 5, 2, 3); baseline near VA, 46 (6, 27, 2, 11); baseline CS letters, 11 (3, 4, 2, 2); baseline reading speed, 79 (14, 45, 3, 17); baseline area of intralesional MA, 4 (—, —, —, 4); final visit BCVA, 42 (24, 14, 1, 3); final visit near VA, 96 (35, 48, 2, 11); final visit CS letters, 64 (39, 27, 1, 6); final visit reading speed, 122 (40, 59, 5, 18); final visit area of intralesional MA, 4 (—, —, 0, 4).
*Vision classed as too poor to read if near VA = 1.6.

The previous findings in the IVAN and CATT trials of more MA with more frequent treatment have not been replicated in our carefully conducted analysis with revised grading definitions. We found no significant associations of the incidence or progression of intralesional MA over 2 years with numbers of injections (fitted as treatment cycles) or drug used. Other smaller studies have addressed this question. Abdelfattah et al[10] reported that the total number of injections predicted the enlargement of MA in 54 eyes, but not the development of new MA. A further study from the same group in 88 eyes treated with ranibizumab detected no relationship between MA development and fixed monthly dosing versus treat-and-extend regimens.[11] The definitions for MA and its location were specified in our protocol before regrading the original trial images. Grading was conducted by trained personnel in the setting of a large well-established reading center. We elected to use the term *intralesional MA*, rather than GA, to describe atrophy that occurred within the nAMD lesion boundaries.

The determination of MA within the boundaries of the neovascular lesion presents a number of challenges. The altered retinal morphologic features arising from the presence of intraretinal and subretinal fluid; fibrosis; and pigment epithelial detachments, tears, or both interfered with the visibility of choroidal vessels and the clear determination of the boundaries of atrophy both within and outside the lesion. However, all available imaging methods, including OCT scans, were used to identify areas of outer retinal and RPE loss. Grading reproducibility was monitored carefully throughout by concordance and training exercises, and a senior grader (B.H.) reviewed all grading decisions when intralesional MA was recorded as present at the baseline visit and at the visit where incident intralesional MA was detected.

We published the findings of the IVAN trial in 2015 and reported an overall rate of incident GA in study eyes of 30% (177/596).[1] These rates were higher than in CATT, in which 187 of 1024 eyes with assessable images (18.3%) demonstrated GA. In CATT, by removing 82 eyes which showed GA at baseline and 79 with missing or unknown GA status, the proportion rose to 106 of 526 eyes (20.2%).[5] In both the IVAN and CATT studies, the diagnosis of GA was based on grading of color fundus photographs (CFPs) of any areas that fitted the criteria for GA without reference to lesion location. Eyes were classified as having GA when CFPs showed 1 or more of these additional characteristics: sharply demarcated borders seen in CFPs, FA, or both; visibility of underlying choroidal vessels; excavated or punched-out appearance on stereoscopy of CFPs or FA; or uniform hyperfluorescence bounded by sharp borders on late-phase angiography. Eligibility criteria excluded the opportunity for GA to involve the fovea in both analyses.[6]

We modelled the ORs of morphologic and functional risk factors studied in the previous literature and in IVAN and CATT. We identified some protective factors for the development of atrophy within the lesion. Predominantly classic CNV at baseline reduced the risk of development or progression of atrophy within the lesion. This may be because of better access to the CNV by anti-VEGF therapy; classic or type 2 CNV typically is considered to be anterior to the RPE. However, a greater effect on the RPE could be seen by the drug, the lesion, or both for lesions predominately under the RPE.

The presence of SRF at the final visit was associated with over a halving of the odds of intralesional MA developing at the final visit (OR, 0.41; $P = 0.004$). Here, SRF at final visit is a proxy variable for persistent SRF during the follow-up period, suggesting that it may be protective. This finding is consistent with those of CATT and HARBOR.[12] Two secondary analyses also support a protective effect of this proxy variable for secondary outcomes: for incident or progressed intralesional MA, the OR for presence of SRF at final visit was 0.36 ($P < 0.001$); for total intralesional MA area, the geometric mean ratio for presence of SRF was 0.66 ($P = 0.20$). Persistent SRF itself may be a protective component or alternatively a sign that the RPE is functioning at least in part by maintaining outer blood−retina barrier function. Sharma at el,[4] in the CATT study, reported better VA at 2 years in eyes with SRF at the foveal center compared with those without SRF (72.8 letters vs. 66.6 letters; $P = 0.006$). This protective effect also was observed in the VEGF Trap VIEW2 study.[13] The situation with intraretinal fluid is less clear. In CATT, but not our study, the presence of intraretinal fluid at 2 years was associated with more GA (OR, 2.10) and worse VA. Like other investigators,[4] we agree that the presence of SRF alone in the absence of intraretinal fluid should not be used to support continued aggressive treatment especially after year 1, and this includes treat-and-extend and pro re nata regimens.

In our study, the presence of PED at baseline was not related to the development or progression of MA. This is in contrast to the recent smaller study from the Treat-and-Extend Age-Related Macular Degeneration Study Group in which PED thickness at baseline was a significant predictor of incident MA.[11] However, we did detect an association between presence of PED (defined as elevation of RPE−Bruch's membrane seen on an OCT) at the final visit and less intralesional MA with a similar effect size to that seen for SRF at the final visit. Pigment epithelial detachments tend to indicate type 1 or predominantly sub-RPE lesions with neovascularization ramifying within the sub-PRE space. As suggested by other investigators,[14] it may be the case that sub-RPE neovascularization may confer resistance to RPE atrophy, but further work is required to investigate this.

We studied both prevalent and incident intralesional MA in the fellow eyes of the IVAN participants, as well as study eyes. We noted that prevalent intralesional MA was infrequent at baseline in fellow eyes with neovascular lesions. It can be argued that fellow eyes with existing nAMD lesions should have had a natural history status comparable with that of study eyes at completion, that is, 24 months into the trial. However, the difference was considerable, with only 18% of fellow eyes with established lesions at baseline, almost all without exposure to anti-VEGF treatment, exhibiting prevalent intralesional MA compared with 32% of study eyes on study completion. This difference is supported by a lower incidence of intralesional MA observed in fellow eyes (14% vs. 25%) over the 2-year follow-up period. Although this comparison is not contemporaneous with the duration of nAMD in the 2 eyes, our findings raise concerns that prolonged exposure to anti-VEGF agents may be a risk factor for MA.

The presence of atrophy in one eye gives useful information on the likely future development of atrophy in the other eye. In the study eye, intralesional MA was more likely to be present at the final visit if intralesional MA or GA (extralesional) were present in the fellow eye at baseline (Figs 3 and 4) and if the total area of atrophy was larger (Fig S3, available at www.aaojournal.org). A similar finding was seen in CATT (GA in the fellow eye conferred an OR of 2.07).

Should clinicians and patients be concerned about the effect of MA on visual function? Our findings of no significant relationship between intralesional MA and change in BCVA, near function, or CS in the study eye provide some reassurance. However, we did observe that changes were in the direction of worse visual outcomes in eyes with intralesional MA, and for near VA, the changes were close to significance ($P = 0.07$). In the CATT study, VA was worse in eyes with nongeographic atrophy and GA at 24 months, but the relationship was not investigated independently.[4] Unlike the case of morphologic measures of atrophy, there is an inherent variability in current clinical measures of visual function, making them less likely to detect effects of MA. In addition, people with MA will have developed adaptive strategies such as eccentric viewing, rendering point measures of VA less informative. In considering this question, we need to emphasize the overwhelming evidence of a beneficial effect on vision of anti-VEGF therapy for nAMD. Our OCT imaging protocol (6 radial B-scans) prevented a robust assessment of the relationship between foveal center involvement by MA and visual function. However, we remain concerned that continued long-term exposure, overexposure, or both to anti-VEGF agents may have an adverse impact on function.

In conclusion, it is important for clinicians to recognize that intralesional MA is common in nAMD lesions, with approximately one third of eyes treated with anti-VEGF drugs exhibiting this feature by 24 months. Although the effect of intralesional MA on visual function, at least as measured by current technology, seems to be limited, the longer-term effects remain unknown.

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Footnotes and Financial Disclosures

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HUMAN SUBJECTS: Human subjects were included in this study. Institutional review board or ethics committee approval was obtained (identifier, 07/NIR03/37), the trial was registered (identifier, ISRCTN92166560), and all participants gave informed consent. All research adhered to the tenets of the Declaration of Helsinki.

No animal subjects were included in this study.

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Abbreviations and Acronyms:
BCVA = best corrected visual acuity; **CATT** = Comparison of Age-Related Macular Degeneration Treatments Trials; **CFP** = color fundus photograph; **CI** = confidence interval; **CNV** = choroidal neovascularization; **CS** = contrast sensitivity; **FA** = fluorescein angiography; **FPED** = fibrovascular pigment epithelial detachment; **GA** = geographic atrophy; **IVAN** = Inhibition of VEGF in Age-Related Choroidal Neovascularisation; **MA** = macular atrophy; **nAMD** = neovascular age-related macular degeneration; **OR** = odds ratio; **PED** = pigment epithelial detachment; **RPE** = retinal pigment epithelium; **SRF** = subretinal fluid; **VA** = visual acuity; **VEGF** = vascular endothelial growth factor.

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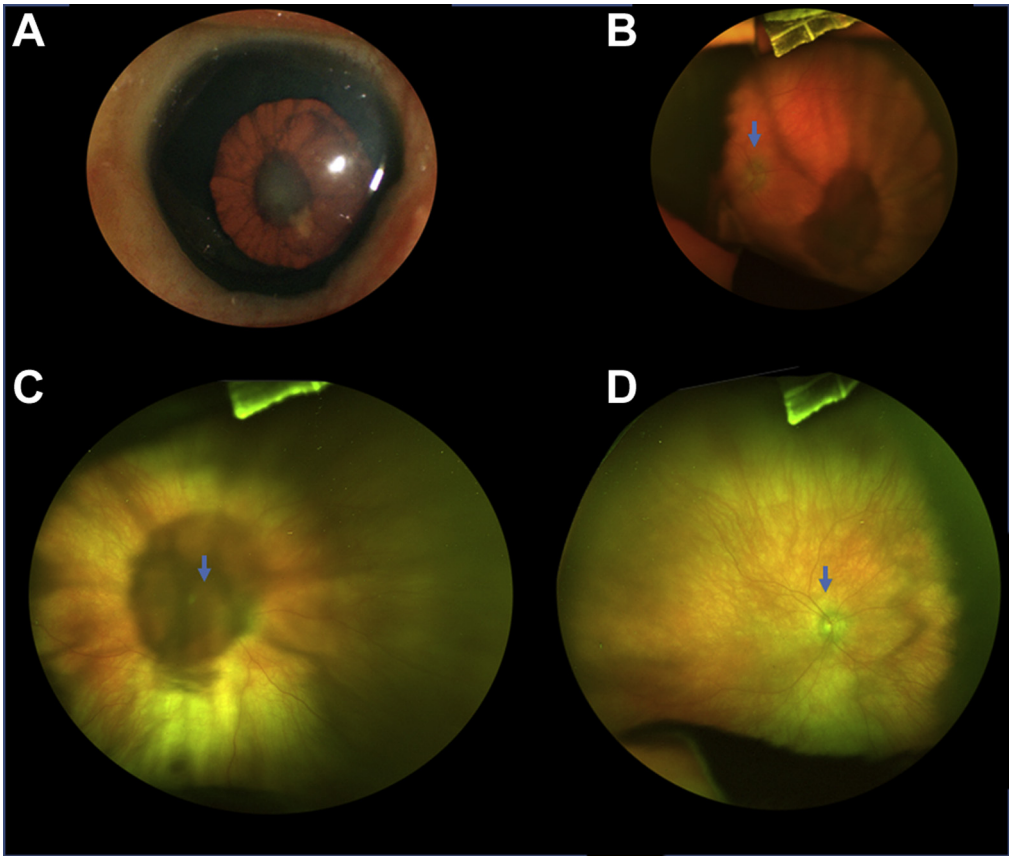
Pictures & Perspectives



Retinopathy of Prematurity Status: Invisible with Indirect Ophthalmoscopy but Established with Optos Ultrawide-Field Retinal Imaging

Indirect ophthalmoscopy by an expert failed to visualize the retina because of lens opacity and tunica vasculosa lentis (**A**) in a 34-week-old child born at 27 weeks and weighing 1000 grams. The Optos California (Dunfermline, Scotland) has a 0.3-mm scanning laser beam that is scattered less than achromatic light and has a virtual focal point behind anterior surface of the lens. (**B**) The field of view increased as the flying baby position approximated the eye to the camera. Cataract artefact blocked the disc (**C**, *blue arrow*), and when the scanning beam entered the eye in an adjacent clear zone (**D**), retinopathy of prematurity was absent. (Magnified version of Fig 1**A**-**D** is available online at www.aaojournal.org).

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